swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

JYNNEOS

International non-proprietary name: modified vaccinia Ankara virus, live attenuated

Pharmaceutical form: suspension for injection

Dosage strength(s): no less than 500 million units

Route(s) of administration: subcutaneous

Marketing authorisation holder: Bavarian Nordic Switzerland AG

Marketing authorisation no.: 69173

Decision and decision date: approved on 1 March 2024

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
Mpox	Monkeypox
MRHD	Maximum recommended human dose
MVA-BN	Modified Vaccinia Ankara – Bavarian Nordic
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for live attenuated modified vaccinia Ankara virus, in the above-mentioned medicinal product.

2.2 Indication and dosage

2.2.1 Requested indication

Active immunisation against disease caused by smallpox, monkeypox, and vaccinia virus in adults (see *Warnings and precautions* and *Pharmacodynamics*).
This vaccine must be used in accordance with the official recommendations.

2.2.2 Approved indication

Active immunisation against disease caused by smallpox, monkeypox, and vaccinia viruses in adults 18 years of age and older (see *Warnings and precautions* and *Pharmacodynamics*).
This vaccine must be used in accordance with the official recommendations.

2.2.3 Requested dosage

Summary of the requested standard dosage:

- *Primary vaccination (individuals previously not vaccinated against smallpox, monkeypox, or vaccinia viruses):* 2 doses of 0.5 mL each should be given by subcutaneous injection at least 28 days apart
- *Booster vaccination (individuals previously vaccinated against smallpox, monkeypox, or vaccinia viruses):* There are inadequate data to determine the appropriate timing of booster doses. If a booster dose is considered necessary, then a single dose of 0.5 mL should be administered s.c.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	23 December 2022
Formal control completed	3 January 2023
List of Questions (LoQ)	3 May 2023
Response to LoQ	31 July 2023
Preliminary decision	26 October 2023
Response to preliminary decision	5 December 2023
Final decision	1 March 2024
Decision	approval

3 Medical context

Mpox (formerly referred to as monkeypox) is a viral zoonotic disease that occurs primarily in tropical rainforest areas of Central and West Africa and is occasionally exported to other regions. It is caused by the monkeypox virus, an enveloped double-stranded DNA virus member of the *Orthopoxvirus* genus in the family *Poxviridae*. The clinical presentation of mpox resembles that of smallpox, a related *Orthopoxvirus* infection which was declared eradicated worldwide in 1980, albeit with a milder presentation. With the subsequent cessation of smallpox vaccination (discontinued in Switzerland in 1972), mpox has emerged as the most important *Orthopoxvirus* for public health.

Mpox is less contagious than smallpox. Human transmission essentially happens through close contact with lesions, body fluids, respiratory droplets, and fomites contaminated by an infected person. The incubation period is typically 1 week (range of 5 to 21 days). Clinical disease is generally self-limited with symptoms lasting from 2 to 3 weeks. The usual clinical manifestations are fever with adenopathy followed within 1-2 days by a skin rash that starts as macular and then progresses to vesicles and pustules. Severe cases rarely occur, most frequently in immunocompromised patients, newborns, and pregnant women. The case fatality ratio of the current 2022 epidemic is approximately 0.1%.

Since early May 2022, cases of mpox have been reported in countries where the disease is not endemic, primarily in Europe and North America. The majority (but not exclusively) involved men who have sex with men. In Switzerland, after the peak of infections in July-August 2022, there has been a sharp decline in confirmed cases, with very few reported since November 2022. As of 4 April 2023, the total number of confirmed cases in Switzerland is 552. There have been no deaths.

Vaccines used for smallpox eradication also provided some protection against mpox, and new generations of vaccines have subsequently been developed. Jynneos is a third-generation live vaccine produced from the strain Modified Vaccinia Ankara-Bavarian Nordic, an attenuated, non-replicating *Orthopoxvirus*.

Vaccination is essentially recommended as pre-exposure for individuals at high-risk, whether in the private sphere or at work (e.g. healthcare and laboratory workers), but can also be used in a post-exposure setting.

4 Quality aspects

4.1 Drug substance

The drug substance consists of purified Modified Vaccinia Ankara – Bavarian Nordic (MVA-BN®) virus which is a highly attenuated *Orthopoxvirus* strain.

Production is based on a seed-lot system. The MVA-BN® virus is propagated in primary chicken embryo fibroblast (CEF) cells derived from a flock free from specified pathogens (SPF), harvested, subjected to ultrasonication, and purified and concentrated by centrifugation and several ultrafiltration/diafiltration steps, including a DNA enzymatic digestion, under strictly aseptic manufacturing conditions.

The MVA-BN® strain was shown to be extremely stable with regards to its genetic, phenotypic, and immunogenic characterisation profile. Release testing includes identity, appearance, pH, endotoxins, sterility, infectious virus titre, genomic quantification, total protein, host-cell (CEF) protein and DNA, and residual benzonase, gentamicin, and ciprofloxacin. Batch analysis data of commercial scale batches indicate a consistent manufacturing process. The analytical methods are described and have been validated in accordance with ICH guidelines.

The drug substance is stored frozen at -50ºC in single-use containers. A shelf life of 82 months has been accepted.

4.2 Drug product

The drug product is provided as a single-use, sterile, liquid frozen suspension in a 2 mL vial containing a dose of 0.5 mL with not less than 5 x 10^7 Infectious Units (Inf. U) of MVA-BN®. The formulation does not contain any adjuvants or preservatives.

The drug product manufacturing process consists of thawing the drug substance and, formulation of the drug substance by mixing with the formulation buffer to produce final bulk vaccine. The final bulk vaccine is filled, inspected, labelled, and packaged. Process validation studies were conducted at commercial scale.

The specifications for release include identity, appearance, pH, extractable volume, osmolality, sterility, bacterial endotoxins, total protein, and virus titre. The stability specification includes identity, appearance, pH, sterility, virus titre, and container closure integrity. All analytical methods are compendial and validated in accordance with ICH guidelines. Batch analysis data were provided at commercial scale.

The container closure system for the final drug product consists of a type I glass vial with a latex-free stopper and a flip off seal.

The final drug product is stored frozen. A decrease of virus titre is observed over the shelf life. A shelf life of 3 years has been accepted if stored at -20°C. A shelf life of 5 years has been accepted if stored at -50°C. A shelf life of 9 years has been accepted if stored at -80°C. The in-use shelf-life claimed for the thawed product is up to 2 months if stored at 2°C to 8°C in the dark. Once thawed the product should not be frozen again.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

5 Nonclinical aspects

Regarding the marketing authorisation application for Jynneos the Division Nonclinical Assessment conducted an abridged evaluation, which was based on the EMA assessment reports dated 30 May 2013 and 21 July 2022 provided by the applicant.

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Jynneos in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. There were no safety issues identified in the nonclinical studies that would be of concern for human use. All nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals.

6 Clinical aspects

The evaluation of the clinical data of this application has been carried out in reliance on previous regulatory decisions by the EMA (EMA/655793/2022, EMA/369203/2013) and FDA (STN 125678/0). The available assessment reports and according product information from these authorities were used as a basis for the clinical evaluation.For further details concerning clinical pharmacology, dosing recommendations, efficacy, and safety, see the annex of this report (information for healthcare professionals).

6.1 Final clinical benefit-risk assessment

The benefit-risk balance of Jynneos for immunisation against smallpox, mpox, and vaccinia has been considered positive by the EMA. The overall benefit-risk assessment for the same indications has therefore been carried out in reliance on previous regulatory decisions by the EMA. A focused benefit-risk assessment from Swissmedic on the mpox indication is provided below.

Beneficial effects and associated uncertainties

Immunogenicity data in humans from the earlier studies POX-MVA-005 and POX-MVA-023 indicate that the vaccinia-specific antibody response peaked 2 weeks after the second dose of vaccine and then declined, with subjects who received a booster at 2 years developing a rapid and strong antibody response. For reasons related to the rarity of the disease before the 2022 outbreak, there are no human clinical efficacy data in the form of randomised controlled trials available regarding Jynneos for mpox prevention. Efficacy is essentially inferred from animal studies in rodents and non-human primates that were part of the non-clinical package. An uncontrolled cohort study monitored by the US Center for Disease Control and Prevention in the Democratic Republic of the Congo indicated that within a 2-year follow-up period, no cases of mpox disease were reported in 1397 healthy, at-risk adult healthcare workers who received 2 doses of the vaccine, contrasting with an expected 5 cases based on historical incidence data. In this cohort, immunogenicity results from 999 participants indicated that 2 weeks after the second vaccine dose, seroconversion to vaccinia was observed in 98% of participants. In an observational prospective cohort study by Public Health England, out of 89 healthcare workers considered as intermediate or high-risk who received Jynneos for pre- or post-exposure prophylaxis against mpox during the 2018 UK outbreak, 1 worker developed mpox. A prospective non-interventional multicentre cohort study to investigate the safety and efficacy of Jynneos against mpox in at-risk individuals in Germany (SEMVAc) within the context of the current mpox outbreak is ongoing as a post-authorisation efficacy study, with the EMA as sponsor.

Unfavourable effects and associated uncertainties

In clinical trials, Jynneos was well-tolerated with mild to moderate and transient local injection site and systemic reactions (headache, fatigue, myalgia, nausea) being the most common (> 10%). No serious adverse events have been determined to be related to Jynneos. These adverse events are adequately described in the information for healthcare professionals. Because of the 2022 mpox outbreak, more safety data will be collected and discussed by the applicant in subsequent periodic safety update reports.

Benefit-risk balance

Taking into account the currently available efficacy and immunogenicity data in humans as well as the body of evidence from animal studies, as well as the favourable safety profile, the benefit-risk balance of Jynneos to prevent mpox disease in at-risk subjects is considered positive.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Jynneos was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

JYNNEOS

Composition

Active substances

Modified Vaccinia Ankara – Bavarian Nordic live virus (produced in chick embryo cells)

Excipients

Trometamol, Sodium chloride, Water for injections

One 0.5 mL dose contains 1.6 mg sodium.

Residues from the manufacturing process: chicken protein, benzonase, gentamicin and ciprofloxacin

Pharmaceutical form and active substance quantity per unit

Suspension for subcutaneous injection.
Light yellow to pale white, milky suspension.
One dose (0.5 mL) contains:
Modified Vaccinia Ankara – Bavarian Nordic live virus, no less than 5 x 107 Inf.U.*

infectious units

Indications/Uses

Active immunisation against disease caused by smallpox, monkeypox and vaccinia viruses in adults 18 years of age and older (see *Warnings and precautions* and *Pharmacodynamics*).

This vaccine must be used in accordance with the official recommendations.

Dosage/Administration

Primary vaccination (for individuals not previously vaccinated against smallpox, monkeypox or vaccinia viruses)

A first dose of 0.5 mL should be administered on the selected date.
A second dose of 0.5 mL should be administered no earlier than 28 days after the first dose, see *Warnings and precautions* and *Pharmacodynamics*.

Booster vaccination (for individuals who have already been vaccinated previously against smallpox, monkeypox or vaccinia viruses)

Insufficient data are available to determine the appropriate timing for the administration of booster doses. If a booster dose is considered necessary, a single dose of 0.5 mL should be administered, see *Warnings and precautions* and *Pharmacodynamics*.

Children and adolescents

The safety and efficacy in children and adolescents under 18 years have not been demonstrated. No data are available.

Special patient groups

Immunocompromised patients (e.g. patients with HIV infection, patients under immunosuppressants) who have already been vaccinated previously against smallpox, monkeypox or vaccinia viruses receive two booster doses. The second booster vaccination must be given no earlier than 28 days after the first booster dose.

Mode of administration

Immunisation is carried out by means of subcutaneous injection, preferably into the upper arm. For instructions on administration, see *Instructions for handling*.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed under *Composition* or to trace residues (chicken protein, benzonase, gentamicin and ciprofloxacin).

Warnings and precautions

Traceability

In order to improve the traceability of biological medicinal products, the name of the medicinal product and the batch number of the medicinal product administered must be documented clearly.

Hypersensitivity and anaphylaxis

As with all vaccines for injection, facilities for appropriate medical treatment and supervision must be available at all times in the rare event of anaphylactic reactions to administration of the vaccine.

Concomitant illness

Immunisation should be postponed where individuals have an acute severe febrile illness or acute infection. In the presence of a minor infection and/or low-grade fever, it is not necessary to postpone the vaccination.

General recommendations

JYNNEOS must not be administered by intravascular injection.

Limitations of vaccine effectiveness

The protective effects of JYNNEOS against disease caused by smallpox, monkeypox and vaccinia viruses has not been studied in humans, see *Pharmacodynamic*s.
A complete protective immune response may not be elicited in all vaccinees.
Insufficient data are available to determine the appropriate timing for the administration of booster doses.
Prior vaccination with JYNNEOS may modify the cutaneous reaction ('take') to subsequently administered replication-competent smallpox vaccines, resulting in a reduced or absent take, see *Pharmacodynamics*.

Individuals with atopic dermatitis

Local and general reactions developed to a greater extent in individuals with atopic dermatitis after vaccination (see *Undesirable effects*).

Immunosuppressed individuals

Data have been collected from HIV-infected individuals with CD4 counts of ≥ 100 cells/µL and ≤ 750 cells/µL. These indicate a lower immune response in HIV-infected than in healthy individuals (see *Pharmacodynamics*). No data are available on the immune response to JYNNEOS in other immunocompromised individuals.
Administration of two doses of JYNNEOS 7 days apart resulted in lower immune responses and slightly more pronounced local reactogenicity than two doses administered 28 days apart. Dosing intervals of less than 28 days are therefore to be avoided.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that it to say essentially 'sodium-free'.

Interactions

No studies have been carried out to document interactions with other vaccines or medicinal products. JYNNEOS should not therefore be administered simultaneously with other vaccines.
Concomitant administration of the vaccine with immunoglobulins, including Vaccinia Immune Globulin (VIG), has not been studied and should be avoided.

Pregnancy, lactation

Pregnancy

There is only very limited experience to date (fewer than 300 pregnancy outcomes) with the use of JYNNEOS in pregnant women. Animal studies revealed no evidence of direct or indirect harmful effects in relation to reproductive toxicity (see *Preclinical data*). As a precautionary measure, use of

JYNNEOS should be avoided during pregnancy. Administration of JYNNEOS during pregnancy should be considered only if the potential benefit outweighs any potential risk to mother and fetus.

Lactation

It is not known whether JYNNEOS is excreted in human milk. As a precautionary measure, use of JYNNEOS should be avoided during breast-feeding. Administration of JYNNEOS during breast-feeding should be considered only if the potential benefit outweighs the possible risks to mother and baby.

Fertility

Animal studies revealed no evidence of impairment of female or male fertility.

Effects on ability to drive and use machines

No relevant studies have been conducted.
However, some of the adverse effects mentioned in *Undesirable effects* might interfere with the ability to use machines (e.g. dizziness).

Undesirable effects

Summary of the safety profile

The safety of JYNNEOS has been assessed in 20 clinical trials in which 5261 vaccinia-naive individuals received two doses of no less than 5 x 10^7 Inf.U. four weeks apart, while 534 vaccinia- and JYNNEOS-experienced individuals received a single booster dose.
The adverse reactions reported most frequently in clinical trials were injection site reactions and the systemic reactions typical of vaccines, which were of mild-to-moderate severity and resolved without treatment within seven days following vaccination.
The adverse reaction rates reported after the individual vaccine doses (1st dose, 2nd dose or booster dose) were similar.

List of adverse reactions

The adverse reactions are arranged according to MedDRA system organ classes and frequency based on the following convention:
"very common" (≥1/10), "common" (≥1/100, <1/10), "uncommon" (≥1/1000, <1/100), "rare" (≥1/10,000, <1/1000)

Table 1: Adverse reactions reported in completed clinical trials with JYNNEOS (n = 7082 subjects)

MedDRA System Organ Class	**Very common (≥1/10)**	**Common (≥1/100, <1/10)**	**Uncommon (≥1/1000, <1/100)**	**Rare (≥1/10,000, <1/1000)**
Infections and	-	-	Nasopharyngitis	Sinusitis

MedDRA System Organ Class	Very common (≥1/10)	Common (≥1/100, <1/10)	Uncommon (≥1/1000, <1/100)	Rare (≥1/10,000, <1/1000)
infestations			Upper respiratory tract infections	Influenza Conjunctivitis
Blood and lymphatic system disorders	-	-	Lymphadenopathy	-
Metabolism and nutrition disorders	-	Appetite disorders	-	-
Psychiatric disorders	-	-	Sleep disorders	-
Nervous system disorders	Headache (30%)	-	Dizziness Paraesthesia	Migraine Peripheral sensory neuropathy Somnolence
Ear and labyrinth disorders	-	-	-	Vertigo
Cardiac disorders	-	-	-	Tachycardia
Respiratory, thoracic and mediastinal disorders	-	-	Pharyngolaryngeal pain Rhinitis Cough	Oropharyngeal pain
Gastrointestinal disorders	Nausea (14%)	-	Diarrhoea Vomiting	Dry mouth Abdominal pain
Skin and subcutaneous tissue disorders	-	-	Rash Pruritus Dermatitis	Urticaria Skin discolouration Hyperhidrosis Bruising Night sweats Subcutaneous nodules Angioedema
Musculoskeletal and connective tissue disorders	Myalgia (32%)	Limb pain Arthralgia	Musculoskeletal stiffness	Back pain Neck pain Muscle spasms Musculoskeletal pain Muscle weakness
General disorders and administration site conditions	Injection site pain (80%) Injection site erythema (63%) Injection site swelling (45%)	Rigor/chills Injection site nodules Injection site discolouration Injection site haematoma	Underarm swelling Malaise Injection site bleeding Injection site irritation	Axillary pain Injection site exfoliation Injection site inflammation Injection site paraesthesia

MedDRA System Organ Class	Very common (≥1/10)	Common (≥1/100, <1/10)	Uncommon (≥1/1000, <1/100)	Rare (≥1/10,000, <1/1000)
	Injection site induration (43%) Injection site pruritus (35%) Fatigue (30%)	Injection site warmth	Facial flushing Chest pain	Injection site reaction Injection site rash Peripheral oedema Asthenia Injection site anaesthesia Injection site dryness Restricted movement at the injection site Flu-like illness Injection site blistering
Investigations	-	Body temperature increased Pyrexia	Troponin I increased Liver enzymes increased White blood cell count decreased Mean platelet volume decreased	White blood cell count increased
Injury, poisoning and procedural complications	-	-	-	Contusion

Description of specific adverse reactions

Individuals with atopic dermatitis (AD)

In a non-placebo-controlled clinical trial comparing the safety of JYNNEOS in individuals with AD and in healthy individuals, individuals with AD reported erythema (61.2%) and swelling (52.2%) at the injection site more frequently than healthy individuals (49.3% and 40.8% respectively). The following general symptoms have been observed more frequently in individuals with AD than in healthy individuals: headache (33.1% vs 24.8%), myalgia (31.8% vs 22.3%), chills (10.7% vs 3.8%), nausea (11.9% vs 6.8%), and fatigue (21.4% vs 14.4%).
7% of the individuals with AD in clinical trials with JYNNEOS experienced a flare-up or worsening of their skin condition during the course of the trial.

Rash

JYNNEOS may trigger local rashes or more widespread eruptions. Events in the form of a rash after vaccination (such cases have been observed in 0.4% of subjects) with JYNNEOS tend to occur within the first few days after vaccination, are of mild-to-moderate severity and usually resolve without complications.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

No cases of overdose have been reported.

Properties/Effects

ATC code

J07BX

Mechanism of action

JYNNEOS is an attenuated, live, non-replicating smallpox and monkeypox vaccine that elicits humoral and cellular immune responses to orthopoxviruses.

Pharmacodynamics

Efficacy in animals

Studies with non-human primates (NHPs) have shown that vaccination with JYNNEOS induces a similar immune response and protective effect to traditional smallpox vaccines used to eradicate smallpox and protected NHPs from severe disease associated with lethal monkeypox virus challenge. As also with traditional smallpox vaccines, a significant reduction in mortality and morbidity (viral load, weight loss, number of pox lesions, etc.) occurred in NHPs vaccinated with JYNNEOS compared with non-vaccinated controls.
Studies in mice have shown that vaccination with JYNNEOS protects mice against lethal replicating vaccinia virus challenge.

Clinical efficacy

Immunogenicity

Seroconversion to vaccinia in vaccinia-naive healthy and special populations

The vaccinia-naive study population included healthy individuals as well as individuals with HIV infection and AD who received 2 doses of JYNNEOS 4 weeks apart. Seroconversion in vaccinia-naive individuals was defined as appearance of vaccinia antibody titres equal to or greater than the assay cut-off value after receipt of 2 doses of JYNNEOS. The seroconversion rates for ELISA and PRNT are presented below:

Table 2: Seroconversion rates in vaccinia-naive healthy and special populations according to ELISA

SCR - ELISA			**Day 7/14[1]**	**Day 28[1]**	**Day 42[1]**
Study	**Health status**	**N**	**SCR % (95% CI)**	**SCR % (95% CI)**	**SCR % (95% CI)**
POX-MVA-005[2]	Healthy	183	70.9 (63.7, 77.4)	88.9 (83.4, 93.1)	98.9 (96.0, 99.9)
POX-MVA-008[3]	Healthy	194	12.5 (8.1, 18.2)	85.4 (79.6, 90.1)	98.5 (95.5, 99.7)
	AD	257	22.9 (17.8, 28.6)	85.4 (80.5, 89.5)	97.3 (94.5, 98.9)
POX-MVA-009[4]	Healthy	66	69.7 (57.1, 80.4)	72.2 (60.4, 83.0)	96.8 (89.0, 99.6)
POX-MVA-011[2]	Healthy	88	29.6 (20.0, 40.8)	83.7 (74.2, 90.8)	98.7 (93.1, 100)
	HIV	351	29.2 (24.3, 34.5)	67.5 (62.1, 72.5)	96.2 (93.4, 98.0)
POX-MVA-013[2]	Healthy	2119[6]	Not determined[5]	Not determined[5]	99.7 (99.4; 99.9)

Table 3: Seroconversion rates in vaccinia-naive healthy and special populations for PRNT

SCR - ELISA			**Day 7/14[1]**	**Day 28[1]**	**Day 42[1]**
Study	**Health status**	**N**	**SCR % (95% CI)**	**SCR % (95% CI)**	**SCR % (95% CI)**
POX-MVA-005[2]	Healthy	183	45.1 (37.7, 52.6)	56.7 (49.1, 64.0)	89.2 (83.7, 93.4)
POX-MVA-008[3]	Healthy	194	5.4 (2.6, 9.8)	24.5 (18.6, 31.2)	86.6 (81.0, 91.1)
	AD	257	5.6 (3.1, 9.3)	26.8 (21.4, 32.7)	90.3 (86.0, 93.6)
POX-MVA-009[4]	Healthy	66	12.1 (5.4, 22.5)	10.6 (4.4, 20.6)	82.5 (70.9, 90.9)

SCR - ELISA			Day 7/14[1]	Day 28[1]	Day 42[1]
Study	**Health status**	**N**	**SCR % (95% CI)**	**SCR % (95% CI)**	**SCR % (95% CI)**
POX-MVA-011[2]	Healthy	88	11.1 (5.2, 20.0)	20.9 (12.9, 31.0)	77.2 (66.4, 85.9)
	HIV	351	15.7 (11.9, 20.1)	22.5 (18.1, 27.4)	60.3 (54.7, 65.8)
POX-MVA-013[2]	Healthy	2119[6]	Not determined[5]	Not determined[5]	99.8 (99.5; 99.9)

[1] Day 7/14 corresponds to 1 or 2 weeks after the first JYNNEOS dose (analysis time point at day 7 only in studies POX-MVA-008 and POX-MVA-011; in POX-MVA-005, the first post-vaccination analysis was performed at day 14); day 28 corresponds to 4 weeks after the first JYNNEOS dose; day 42 corresponds to 2 weeks after the second JYNNEOS dose; SCR = seroconversion rate; PRNT = plaque reduction neutralisation test; ELISA = enzyme-linked immunosorbent assay using MVA as an antigen; [2] Full Analysis Set (FAS (for POX-MVA-013: Immunogenicity Analysis Set; IAS); [3] Per Protocol Analysis Set (PPS), [4] seropositivity rates, [5] no immunogenicity sample taken, [6] combined groups 1-3.

Seroconversion rates to vaccinia in vaccinia-experienced healthy and special populations

Seroconversion in vaccinia-experienced individuals was defined as at least a two-fold increase in baseline titres following a single vaccination with JYNNEOS.

Table 4: Seroconversion rates in vaccinia-experienced healthy and special populations for ELISA

SCR - ELISA			Day 0[1]	Day 7/14[1]	Day 28[1]	Day 42[1]
Study	**Health status**	**N**	**SCR %**	**SCR % (95% CI)**	**SCR % (95% CI)**	**SCR % (95% CI)**
POX-MVA-005[2]	Healthy	200	-	95.5 (91.6, 97.9)	93.0 (88.5, 96.1)	Not applicable
POX-MVA-024[2]	Healthy	61	-	83.6 (71.9, 91.8)	79.7 (67.2, 89.0)	Not applicable
POX-MVA-011[2]	Healthy	9	-	62.5 (24.5, 91.5)	100 (63.1, 100)	100 (59.0, 100.0)
	HIV	131	-	57.3 (48.1, 66.1)	76.6 (68.2, 83.7)	92.7 (86.6, 96.6)

Table 5: Seroconversion rates in vaccinia-experienced healthy and special populations for PRNT

SCR - ELISA			Day 0[1]	Day 7/14[1]	Day 28[1]	Day 42[1]
Study	**Health status**	**N**	**SCR %**	**SCR % (95% CI)**	**SCR % (95% CI)**	**Study**
POX-MVA-005[2]	Healthy	200	-	78.5 (72.2, 84.0)	69.8 (63.0, 76.1)	Not applicable
POX-MVA-024[2]	Healthy	61	-	73.8 (60.9, 84.2)	71.2 (57.9, 82.2)	Not applicable
POX-MVA-011[2]	Healthy	9	-	75.0 (34.9, 96.8)	62.5 (24.5, 91.5)	85.7 (42.1, 99.6)
	HIV	131	-	46.0 (37.0, 55.1)	59.7 (50.5, 68.4)	75.6 (67.0, 82.9)

[1] Day 0 corresponds to the day of vaccination with JYNNEOS; day 7/14 corresponds to 1 or 2 weeks after vaccination with JYNNEOS (the first post-vaccination analysis was performed at day 7 in study POX-MVA-011, and at day 14 in studies POX-MVA-005 and POX-MVA-024); day 28 corresponds to 4 weeks after vaccination with JYNNEOS; SCR = seroconversion rate; 2 Full Analysis Set (FAS); PRNT = plaque reduction neutralisation test; ELISA = enzyme-linked immunosorbent assay using MVA as an antigen.

Long-term immunogenicity to vaccinia in humans

Only limited data on long-term immunogenicity covering a period of 24 months following primary vaccination of vaccinia-naive individuals with JYNNEOS are currently available.
These are presented below:

Table 6: Seroconversion rates in vaccinia-naive healthy individuals over a period of 24 months for ELISA and PRNT

		ELISA		PRNT	
Month	**N**	**SCR % (95% CI)**	**GMT (95% CI)**	**SCR % (95% CI)**	**GMT (95% CI)**
2	178	98.9 (96.0, 99.9)	328.7 (288.5, 374.4)	86.0 (80.0, 90.7)	34.0 (26.4, 43.9)
6	178	73.0 (65.9, 79.4)	27.9 (20.7, 37.6)	65.2 (57.7, 72.1)	7.2 (5.6, 9.4)
24*	92	71.7 (61.4, 80.6)	23.3 (15.2, 35.9)	5.4 (1.8, 12.2)	1.3 (1.0, 1.5)

ELISA = enzyme-linked immunosorbent assay; GMT= geometric mean titre; n = number of subjects in the specific study group; PRNT = plaque reduction neutralisation test; SKR = seroconversions rate.
* corresponds to seropositivity rates

Booster dose

Two clinical trials have shown that JYNNEOS is capable of boosting a pre-existing immunological memory response to vaccinia, induced by vaccination with authorised smallpox vaccines a long time previously or after vaccination with JYNNEOS 2 years previously.

Table 7: Seroconversion rates after a booster dose for ELISA and PRNT

Primary immunisation		**N**	**Day 0[1]**		**N**	**Day 7[1]**		**Day 14[1]**	
	ELISA		**S+ %**	**GMT**		**S+ %**	**GMT**	**S+ %**	**GMT**
2 doses of JYNNEOS		92	72	23	75	100	738	100	1.688
Authorised smallpox vaccine		200	79	39	195	-	-	98	621
	PRNT		**S+ %**	**GMT**		**S+ %**	**GMT**	**S+ %**	**GMT**
2 doses of JYNNEOS		92	5.4	1	75	92	54	99	125
Authorised smallpox vaccine		200	77	22	195	-	-	98	190

[1] Day 0 corresponds to the day of booster vaccination with JYNNEOS (pre-booster); day 7 and 14 correspond to 1 or 2 weeks after booster vaccination with JYNNEOS; n = number of subjects in the specific study group; ELISA = enzyme-linked immunosorbent assay using MVA as an antigen; PRNT = plaque reduction neutralisation test; S+ = seropositivity rate; GMT = geometric mean titre.

Immunogenicity and attenuation of the cutaneous reaction to ACAM2000 in healthy subjects

JYNNEOS was compared with ACAM2000 (a 'second generation' live attenuated smallpox vaccine obtained from cell culture and authorised in the USA) in a randomised, open-label non-inferiority study in smallpox vaccine-naive healthy subjects (US military personnel) aged 18 to 42 years (study POX-MVA-006). After randomisation in a ratio of 1:1, a total of 433 subjects received either two doses of JYNNEOS followed by a single dose of ACAM2000 at four-week intervals or just a single dose of ACAM2000. ACAM2000 was administered by means of scarification.

The first co-primary endpoint compared the vaccinia-specific neutralising antibody responses at the peak time points (day 42 after first vaccination for JYNNEOS, with the subjects receiving two doses according to the standard vaccination schedule, and day 28 for ACAM2000). JYNNEOS induced a geometric mean titre (GMT) of neutralising antibodies at the peak of 153.5 (n = 185; 95% CI 134.3, 175.6), which is non-inferior to the GMT of 79.3 (n = 186; 95% CI 67.1, 93.8) obtained after scarification with ACAM2000.

The second co-primary endpoint evaluated whether vaccination with JYNNEOS (n = 165) prior to administration of ACAM2000 resulted in attenuation of the cutaneous reaction to ACAM2000 (n = 161),

measured on the basis of the maximum lesion area in mm^2. At day 13–15, ,the median maximum lesion area was 75mm^2 (95-% CI 69.0, 85.0) for the subjects who had received ACAM2000 and 0.0 (95% CI 0.0, 2.0) for those who had received JYNNEOS.

Pharmacokinetics

Absorption

Not applicable.

Distribution

Not applicable.

Metabolism

Not applicable.

Elimination

Not applicable.

Preclinical data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity and reproductive toxicity.

Other information

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack. 3 years at -20 °C ± 5 °C
5 years at -50 °C ± 10 °C
9 years at -80 °C ± 10 °C

Special precautions for storage

Store in the freezer (at -20 °C ± 5 °C or -50 °C ± 10 °C or -80 °C ± 10 °C).
The expiry date depends on the storage temperature. After thawing, the vaccine can be stored for a short time in a dark place before use for up to 2 months within the stated shelf life period in a refrigerator at 2 °C – 8 °C.
Store the container in the outer packaging to protect the contents from light.
Do not refreeze the vaccine after thawing.

Instructions for handling

The vial should be allowed to reach a temperature between 8 °C and 25 °C before use. Swirl the vial gently before use for at least 30 seconds.
The suspension should be inspected visually for particles and discolouration before use. The vaccine must be discarded if the vial is damaged or if the suspension contains foreign particles or displays any other variation in physical appearance. A dose of 0.5 mL is drawn up into a syringe for injection.
Each vial is for single use.
Any unused vaccine or waste material must be disposed of in accordance with national requirements.

Authorisation number

69173 (Swissmedic)

Packs

Pack size of 20 single dose vials [B]

Marketing authorisation holder

Bavarian Nordic Switzerland AG, 6301 Zug, Switzerland

Manufacturer

Bavarian Nordic A/S, 3490 Kvistgaard, Denmark

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